REMARKS

Claims 24-27, 41-42, 49 and 57-62 are under examination and have been rejected. In response, Applicants have amended claims, added new claims 63-66, canceled claims 41 and 42 and make the following remarks:

Request for Continued Examination

Because the present rejection is final, Applicants have included herewith a Request for Continued Examination along with the required fee for a large entity.

Claims

Applicant acknowledges the Examiner's comments regarding claim 24. Applicant has not made any further correction in response thereto because none was requested.

Information Disclosure Statement

In response to the Examiner's comment regarding the 3 cited PCT applications, Applicant herewith submits a Supplemental IDS along with copies of said published PCTs.

Rejection Under 35 U.S.C. §112, ¶2

Claims 24-27, 41-42, 49 and 57-62 were rejected under 35 U.S.C. §112, ¶1, as being indefinite for use of relative terms relating to increasing HDL-C and lipid transport

activity without stating the reference value used for comparison. As noted in the application clinical studies showed that plasma HDL-C concentration was inversely related to coronary artery disease (CAD) and that protective effects of increasing HDL-C occur throughout most of life so that low HDL-C is associated with elevated risk of CAD even where normal total plasma cholesterol levels are observed (these being taken as less than 5.2 mmol/l of plasma) and that CAD risk is increased by 2% in men and 3% in women for every 1 mg/dL (0.026 mmol/l) reduction in HDL-C (see application at page 1, lines 23-31).

From this it is clear that any increase in HDL may be deemed advantageous and not just an increase relative to a stated reference value (such as the accepted normal value) for HDL-C in human plasma because even persons with normal HDL levels may still be at risk. Thus, the invention is drawn to treatment by elevating HDL levels regardless of the existing cholesterol level in the plasma of the patient (i.e., above whatever the current value is for the patient to be treated).

In view of the foregoing, Applicants have amended claim 24 to recite that treatment is of a human patient (supported in the application at page 6, lines 19-24) and that HDL is being elevated over its existing value in the treated patient without regard to a standard normal value. Regarding claim 25, low HDL-C is regarded as that below 0.9 mmol/l and this claim has been amended to so recite (for support, see page 2, lines 10 and 18-19 of the application). Claim 24 has also been amended to indicate that the change is by at least 10% (see application at page 14, lines 18-22). Applicant has also added new claims 63 and 64 drawn to increases of 25% and 50%, respectively, over claim 24 (also supported in the application at page 14, lines 18-22). Other claims have been canceled or amended to remove reference to treatment of other than a human.

Rejection Under 35 U.S.C. §112, ¶1

Claims 24-27, 41-42, 49 and 57-62 were rejected under 35 U.S.C. §112, ¶1, as failing to meet the written description requirement on grounds that they contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (i.e., a new matter rejection).

In particular, claim 24 was rejected for use of the term "ABC1-mediated lipid transport activity" and for claiming increasing HDL-C by increasing said activity. In response, Applicants have amended claim 24 to delete the term "mediated" and just recite "ABC1 lipid transport activity." In view of this amendment, Applicants believe that this ground of rejection has been overcome and respectfully request that it be withdrawn.

Claim 25 was rejected for reciting a cardiovascular disease associated with low HDL-C whereas the application indicates this as a risk factor. In response, claim 25 has been amended to recite risk of cardiovascular disease.

Claims 24-27, 41-42, 49 and 57-62 were also rejected under 35 U.S.C. 112, first paragraph, for failing to meet the written description requirement based on the decision in University of Rochester v. G.D. Searle and Co. (69 USPQ2d 1886) in that the claims are drawn to treating a disease with a genus of compounds defined in the claim solely by their function while the specification and prior art fail to recite such a compound. The Examiner also notes that claims 57-62 were added by preliminary amendment, with support cited at pages 1, 9 and 76. The Examiner contends that page 1 teaches a correlation between HDL-C and cardiovascular disease, that page 9 teaches a method for screening a compound for use in treatment of low HDL-C, and that page 76 "states that agents that modulate ABCA1 biological activity can be used to treat cardiovascular disease OR low HDL-C" apparently contradicting "applicant's assertion that this disclosure supports the claimed method." (see page 6 of the Office Action)

In response, Applicants reiterate previous arguments but also add that the U. of Rochester case is inapposite to the present invention. In Rochester, the application was drawn to treatment claims using compounds that inhibited the recited target. In the present case, Applicants are not claiming treatment by inhibiting a target (which inhibition could be by any compound yet to be discovered, as in Rochester) but, rather, treatment by increasing lipid transport activity by ABC1. While merely providing screening claims for inhibitors might not, under Rochester, support their use in treatment claims (or any other method claims), claims to increasing activity are different because in disclosing the target the inventor is inherently disclosing a compound that increases the activity. Thus, Applicants provide a number of sequences that increase ABC1 lipid-transport activity because they have such activity.

The invention provides methods of treating a human having low HDL cholesterol or a cardiovascular disease, or at risk thereof, by administering to the human patient, an effective amount of an ABC1 polypeptide, or cholesterol-regulating fragment thereof, where the patient has a low HDL cholesterol level relative to normal. This ABC1 polypeptide could be the wild-type human ABC1, or have a mutation that increases its stability or its activity in the regulation of cholesterol (application at page 6, lines 19-27). The Examiner concedes that increasing ABC1 protein would increase ABC1 transport activity (see Office Action at page 13, last line, over to page 14, line 1).

Further, Applicants disclose in the specification, at pages 77-80, a number of sequence variants useful in the method of the invention. For example, at page 78, lines 7-8, a polypeptide sequence variant associated with "significantly less cardiovascular disease," at page 78, lines 22-24, a polypeptide sequence variant associated with lower coronary artery disease and the same for the variant disclosed at page 78, lines 26-28. Thus, one skilled in the art would expect that the use of such variants should negative the risk of cardiovascular disease in individuals receiving the therapy.

Applicants for the first time define the correct wild type human sequence (SEQ ID NO: 1 for the polypeptide – see application at page 40, line 29, to page 41, line 3) and thus each "mutation containing" sequence is a separate sequence of ABC1. Therefore, Applicants respectfully submit that the specification teaches a number of ABC1 polypeptides that could be used in the methods of the invention.

In addition, those skilled in the art would believe that Applicants were in possession of a large number of ABC1 polypeptides because Applicants already have an issued patent (U.S. Pat. No. 6,617,122) that contains claims drawn to screening assays using a mammalian ABC1 polypeptide with 85% identity to SEQ ID NO: 1 and having lipid transporting activity. Thus, Applicants, at the time of their invention, certainly contemplated, and were in possession of, numerous ABC1 polypeptides having the desired activity because any polypeptide that could function in such an assay could also prove useful in the methods of the invention.

For example, in administering agents for use in the invention, one might introduce into a patient liposomes comprising ABC1 that could fuse with cells of the patient at risk, thereby increasing ABC1 transporter activity in the cells (see application at page 73, line 18) or the active polypeptides could be administered a different way. Applicants also disclose specific cells that contain high ABC1 activity (see application at page 4, lines 1-4, and at page 27, lines 6-7) so that such cells could be collected from a patient and fused with carriers, such as microsomes, to insert more ABC1 polypeptide into the membranes of the cells. Such methods are well known in the art.

The claims have also been rejected on the basis of insufficient enablement (see office action at pages 8-12). In response, Applicants have amended the claims to better identify the contemplated invention (e.g., clearly reciting that ABC1 transporter activity is to be increased in amended claim 24 as the basis for treatment or reducing risk rather than administration of any specific agents). Further, during prosecution of the parent '122 patent, the Examiner had observed that at the time of this invention the physiological role

of ABC1 was unknown (See the '122 prosecution history, Office Action of 4 June 2002 (Paper No. 16), at page 9, lines 16-18). Thus, prior to Applicants' initial disclosure, no one even knew the role of this protein in human health. As a result, Applicants' contend that the '122 patent (the parent of the present case) is a pioneering patent and Applicants should be entitled to the full breadth of their invention. While drug development is usually time consuming and expensive, it is routine and does not involve undue experimentation. This is reflected in the commercial reality of high value agreements between companies for the identification of new drug discovery targets.

Because Applicants have disclosed agents useful in increasing ABC1 lipid transport activity (e.g., ABC1 polypeptides and fragments) they should be entitled to broad treatment claims without being limited to recited examples of every type of compound that may be useful in increasing such activity.

In addition, the rejection relies in part on the contention that "neither the specification nor the prior art appears to recognize a compound encompassed by claim 24" (see Office Action at page 6, lines 14-15) yet the rejection relies on a number of references purported to anticipate claim 24 (see Office Action at pages 13-16). Applicants also direct the Examiner's attention to withdrawn claims 52-56, which recite numerous agents that mimic wild type ABC1 activity. Because Applicants are claiming treatment by increasing ABC1 activity these agents provide enablement.

Rejection Under 35 U.S.C. §102/103

Claims 24-27, 42, 49, and 59-60 were rejected under 35 U.S.C. 102(b) as being anticipated or, in the alternative, obvious over Smud et al. (1987) as evidenced by Steiner et al (1996) and Arakawa et al. (2005). The Examiner's argument is that the claims "are drawn to a method for treating a mammal having or at risk of developing cardiovascular disease by administering to said mammal a compound that modulates ABCA1 biological

activity." Claim 24 has now been amended to recite treatment of a human patient.

In response, Applicants have amended claim 24 to recite that ABC1 activity by at least 10% in a patient (with dependent claims 63 and 64 reciting at least 25% and 50% in ABC1 activity, respectively, and new claims 65 and 66 increasing plasma HDL-C in said patient by at least 25% and 50%, respectively, all supported in the application at page 14, lines 18-22).

Further, irrespective of the teaching of Steiner et al. and/or Arakawa et al., amended claim 24 requires that the ABC1 activity be increased by at least 10% in the patient. Smud et al. and Steiner et al. do not disclose any increase in ABC1 activity while Arakawa et al. discloses increase in ABC1 in a cell culture using murine cell lines and not in a human patient. Thus, these references do not render claim 24 (or claims dependent from claim 24) anticipated or obvious because they do not teach or imply, separately or in combination, that increased ABC1 activity of at least 10% (or by 25% or 50% recited in new claims 63 and 64) or increased plasma HDL-C by at least 25% or 50% (new claims 65 and 66, respectively) in a patient is therapeutic. At best, they only disclose increases in ABC1 expression in cultured cells where any amount of modulating agent can be administered.

In addition, Arakawa utilizes Wy14643 (a non-clinical PPAR activator – see page 1195, column 2, line 11 from the bottom) as a positive control (see page 1195, column 2, last 2 lines), hypothesizes that Wy14643 increases transcription of ABC1 gene (see page 1195, column 2, line 7 from bottom), finds that fenofibrate and Wy14643 increase ABC1 message in all cells examined (see page 1194, column 1, last 5 lines) but notes that fenofibrate and Wy14643 have been found to have different characteristics between human and murine PPARs (which is the mechanism of action Arakawa discloses) so that, without more, it is unclear what effect a given compound would have in humans. Applicant also include the accompanying Staels et al (1998) paper showing that prior to filing the mechanism of fibrates was believed to rest on secondary lipid metabolic effects

(see page 2089, column 2, bottom).

Claims 24-27, 42, 49, and 57-62 were rejected under 35 U.S.C. 102(b) as being anticipated or, in the alternative, obvious under 103(a), over Hahmann et al. (1991) as evidenced by Arakawa et al. (2005).

In response, Applicants note the amendment to claim 24 and further contend that irrespective of the teaching of Hahmann et al. and/or Arakawa et al., amended claim 24 requires that the ABC1 activity be increased by at least 10% in the patient. Hahmann et al. merely shows a 19% increase in HDL-C but not the at least 25% and 50% increases required by new claims 65 and 6, respectively, or the at least 10% increase in ABC1 activity in the patient. Again, Arakawa et al. only shows an increase in ABC1 in a murine cell culture (regardless of the percent increase) and not in a patient. Thus, these references do not render claim 24 (or claims dependent from claim 24) anticipated or obvious because they do not teach or imply, separately or in combination, that increased ABC1 activity of at least 10% (or by 25% or 50% recited in new claims 63 and 64) or increased plasma HDL-C by at least 25% or 50% (new claims 65 and 66, respectively) in a patient is therapeutic. At best, they only disclose increases in ABC1 expression in cultured cells where any amount of modulating agent can be administered.

Claims 24-27, 42, 49, and 59-60 were rejected under 35 U.S.C. 102(b) as being anticipated or, in the alternative, obvious under 103(a), over Olivier et al. (1988) as evidenced by Mack et al. (1991) and Arakawa et al. (2005).

In response, Applicants again note the amendment to claim 24 and further contend that irrespective of the teaching of Olivier et al. and/or Mack et al. and/or Arakawa et al., separately or in combination, amended claim 24 requires that the ABC1 activity be increased by at least 10% in the patient. Hahmann et al. merely shows a 19% increase in HDL-C but not the at least 25% and 50% increases required by new claims 65 and 6, respectively, (for example, Olivier et al. only recites 23% in ¶2 of the Summary on

the cover page thereof – also noted in the Office Action at ¶18, line 11) or the at least 10% increase in ABC1 activity in the patient. Again, Arakawa et al. only shows an increase in ABC1 in a murine cell culture (regardless of the percent increase) and not in a patient, while Mack et al. only teaches a correlation between high cholesterol and coronary artery disease. Thus, these references do not render claim 24 (or claims dependent from claim 24) anticipated or obvious because they do not teach or imply, separately or in combination, that increased ABC1 activity of at least 10% (or by 25% or 50% recited in new claims 63 and 64) or elevated plasma HDL-C by at least 25% or 50% (new claims 65 and 66, respectively) in a patient is therapeutic. At best, they only disclose increases in ABC1 expression in cultured cells where any amount of modulating agent can be administered.

In view of the amendments to the claims and the above remarks, Applicants believe that the grounds of rejection have been overcome and request reconsideration of the pending claims.

Obviousness-Type Double Patenting

Claims 24-27, 41-45, 49 and 57-62 were provisionally rejected under the doctrine of obviousness-type double patenting over U.S. utility applications 10/479,198, 10/744,465, 10/745,377 and 10/833,679.

Claims 24-28, 42-43, 45 and 57-62 were provisionally rejected under the doctrine of obviousness-type double patenting over claims 23, 24, 26 and 27 of U.S. utility applications 10/479,198 and over claims 26-28 and 32 of U.S. utility applications 10/745,377.

Applicants had previously submitted a terminal disclaimer for both the '198 and '377 applications (as noted on Applicants' transmittal and postcard) and duly paid the

fee for each. The Examiner indicates that he was unable to locate these in the file. Applicants herewith submit copies of these disclaimer forms that were previously submitted. The Examiner is welcome to check the record to confirm that fees have already been paid for these disclaimers.

Claims 24-28, 41-45, 49 and 57-62 were provisionally rejected under the doctrine of obviousness-type double patenting over claims 36-48 of U.S. Application 10/833,679. The indicated claims are drawn to treating low HDL cholesterol or cardiovascular disease by administering a nucleic acid molecule encoding an ABC1 polypeptide or a cholesterol-regulating fragment thereof. In response, Applicants enclose herewith a Terminal Disclaimer for the '679 application.

Applicant has also included herewith a Request for Continued Examination, a request for a 3 month extension of time to respond and the appropriate fees paid by check. The Commissioner is authorized to charge payment of any fees required for this communication or credit any overpayment to Deposit Account No. 03-0678.

EXPRESS MAIL CERTIFICATE

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Deposit Date: 22 August 2007

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Respectfully submitted,

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